San Antonio Breast Cancer Symposium

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Of the many high-interest presentations at the 33rd Annual Cancer Therapy and Research Center–American Association for Cancer Research San Antonio Breast Cancer Symposium, *P&T* reviews two large trials with seemingly contradictory findings on the anti-cancer effects of zoledronic acid, one study on dual blockade of HER-2 with lapatinib and trastuzumab, and another trial of combined everolimus and tamoxifen. Regarding the first two trials, some experts suggest that zoledronic acid's direct effects are not on cancer cells themselves but, instead, on the bone microenvironment. Over 9,000 people from more than 90 countries attended the meeting, which took place from December 8 to 12, 2010.

Conflicting Findings on Bisphosphonates and a Focus on Drug Combinations

Adjuvant Treatment With Zoledronic Acid In Stage II/III Breast Cancer: The AZURE Trial

- Robert E. Coleman, MD, University of Sheffield, Leeds, U.K.
- Sharon H. Giordano, MD, MPH, University of Texas MD Anderson Cancer Center, Houston, Tex., Discussant

The use of zoledronic acid (Zometa, Novartis) was not observed to improve disease-free survival in a broad population of stage II/III breast cancer patients treated with adjuvant chemotherapy in the AZURE (Adjuvant Zoledronic acid to Reduce Recurrence) trial. However, a prespecified subanalysis of disease-free survival and overall survival, based on menopausal status, did show significant benefit for this medication. That finding, said AZURE lead investigator Dr. Coleman, when considered in the light of the recent phase 3 ABCSG-12 (Austrian Breast & Colorectal Cancer Study Group) trial, suggests that "adjuvant bisphosphonate efficacy appears to be dependent on a low estrogen/inhibin concentration within the bone microenvironment."

In ABCSG-12, the addition of three years of zoledronic acid to hormonal therapy following surgery improved disease-free survival by 32%. This trial included 1,800 premenopausal women with hormone receptor–positive, early-stage breast cancer.

AZURE, an open-label, multicenter, parallel-group trial, included 3,360 women with stage II/III breast cancer from 174 centers in seven countries. Participants were randomly assigned to receive neoadjuvant chemotherapy and/or endocrine therapy with or without intravenous (IV) zoledronic acid 4 mg every three to four weeks for six doses, then every three months for eight doses, and six months for five doses, to complete five years of treatment. The primary endpoint was disease-free survival.

Dr. Coleman characterized the AZURE population as relatively high-risk, with about one-third of the women postmenopausal and their ages slightly below that of the average breast cancer population. After a median follow-up of 59 months, there were no differences between the groups in either disease-free survival or invasive disease-free survival (disease-free survival/adjusted hazard ratio [HR] = 0.98; P = 0.79, respectively, and invasive disease-free survival/adjusted HR = 0.98; P = 0.73, respectively).

Dr. Coleman said, "Clearly, our results are very different from ABCSG-12, but actually these two populations are not the same."

He pointed out that in terms of the host, AZURE patients were treated in a high-estrogen environment and ABCSG-12 patients were treated in a low-estrogen environment. That difference was reflected in a further prespecified analysis of disease-free survival from AZURE based on menopausal status.

Among premenopausal women and women who were postmenopausal for less than five years, the odds ratio was 1.13 (0.95–1.35), whereas for women more than five years from menopause, the odds ratio was 0.76 (0.60–0.98), with significant heterogeneity (P = 0.02) noted between the groups.

The overall survival benefit with zoledronic acid was not significant in the overall population (243 deaths in premenopausal women vs. 276 deaths in postmenopausal women; P = 0.07); however, among women who were postmenopausal for more than five years or who were older than 60 years of age (n = 1,101), the overall survival benefit was significant, with 29% fewer deaths (86 deaths in premenopausal patients vs. 120 deaths in postmenopausal patients, respectively; P = 0.017).

"We believe this is due to host differences rather than treatment differences," Dr. Coleman said.

"I would consider this hypothesis-generating and not practice-changing," commented Symposium discussant Dr. Giordano.

Novartis has withdrawn its supplemental marketing authorization applications in the U.S. and Europe for the use of zoledronic acid as adjuvant therapy for premenopausal women with hormone receptor–positive breast cancer. The company is evaluating future plans for this indication in connection with the drug.

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Carry-Over Effect of Adjuvant Zoledronic Acid After 48 and 62 Months: The ABCSG-12 Trial

- Michael Gnant, MD, Medical University of Vienna, Vienna, Austria

The Austrian Breast & Colorectal Cancer Study Group (ABCSG-12) trial examined the efficacy of ovarian suppression using goserelin (Zoladex, AstraZeneca) combined with tamoxifen (Nolvadex, AstraZeneca) or anastrozole (Arimidex, AstraZeneca), with and without zoledronic acid, in premenopausal patients with endocrine-responsive early (stage I or II) breast cancer. All of the women (mean age, 44.5 years) had undergone surgery.

Patients were treated for three years with subcutaneous goserelin 3.6 mg every 28 days. They were randomly assigned to receive oral tamoxifen 20 mg/daily plus placebo, oral anastrozole 1 mg daily plus placebo, or either tamoxifen or anastrozole with IV zoledronic acid 4 mg every six months.

In a previous analysis at a median follow-up of 48 months, adding zoledronic acid to adjuvant endocrine therapy had significantly reduced the risk of disease-free survival events by 36%, compared with endocrine therapy alone (HR = 0.64; $P = 0.01$). In the current report, at a median follow-up of 62 months with 36% more patients with disease-free survival events and more than two years after completing treatment, zoledronic acid continued to reduce the risk of disease-free survival events by 32%, compared with endocrine therapy alone (HR = 0.68; $P = 0.008$). The benefits of zoledronic acid were seen in both the tamoxifen (HR = 0.67) and anastrozole (HR = 0.68) treatment groups.

The trend toward a reduced risk of death (HR = 0.60; $P = 0.11$), observed at a median follow-up of 48 months for adding zoledronic acid to endocrine therapy, persisted in the later (62-month) analysis (HR for death = 0.67; $P = 0.09$ for zoledronic acid vs. no zoledronic acid).

Zoledronic acid did not improve disease-free survival among women 40 years of age or younger (HR = 0.94; $P = 0.821$). However, among women older than 40, disease-free survival was significantly higher with zoledronic acid compared with no zoledronic acid (HR = 0.58; $P = 0.003$). In the same comparison for overall survival, there was a strong trend favoring therapy with zoledronic acid (HR = 0.57; $P = 0.057$).

Serious adverse events with zoledronic acid were not increased, compared with endocrine therapy alone. There was no significant renal toxicity, and there were no confirmed cases of osteonecrosis of the jaw.

"The 62-month analyses, at more than two years after treatment completion, confirm and extend the lasting clinical and anticancer benefits with zoledronic acid reported at the 48-month follow-up of ABCSG-12," Dr. Gnant concluded.

In an interview, he said:

> I believe what's happening with early breast cancer, and probably with cancer in general, is that at the time of diagnosis, and maybe even before the primary tumor is established, there are cancer stem cells in the bone marrow. They can go into a quiescent state with no direct toxic effects. But by a mechanism we don't understand perfectly, probably an imbalance of suppressing and promoting factors, some of them wake up and can re-establish the disease—even 20 years after the initial diagnosis, as we often see in breast cancer.

The effect of bisphosphonates, he continued, is not directly to kill cancer cells but to slow down growth factor release and oxygen support, so that when a dormant cell "wakes up" after 20 years, it has no oxygen and no growth factors and may even go to sleep again or die from apoptosis according to its programming. He added:

> At that stage of the disease, we are not fighting a million cells, as in metastatic cancer. It may be a handful or several dozen. So we just deprive them of what they need to wake up and break out again. By doing so, we may actually achieve a cure, which is a word we should use only very humbly as oncologists.

Lapatinib, Trastuzumab, and Their Combination Plus Paclitaxel for HER-2–Positive Primary Breast Cancer: The Neo-ALTTO Trial

- Jose Baselga, MD, Massachusetts General Hospital, Boston, Mass. (formerly of Vall d'Hebron Hospitals, Barcelona, Spain)
- Eric P. Winer, Dana Farber Cancer Institute, Boston, Mass., Discussant

First results of the Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial show promise for dual blockade of human epidermal growth factor receptor 2 (HER-2) with trastuzumab (Herceptin, Genentech) and lapatinib (Tykerb, GlaxoSmithKline) in breast cancer patients. Earlier research had shown that lapatinib increased the antitumor efficacy of trastuzumab in HER-2–positive (HER-2+) breast cancer models and lapatinib, combined with chemotherapy, improved progression-free survival in both first-line and second-line metastatic HER-2+ breast cancer.

Neo-ALTTO is an international, multicenter, randomized study of neoadjuvant treatment for HER-2+ primary breast cancer among 455 patients from 99 sites. Participants received lapatinib 1,500 mg/day (154 patients); or a loading dose of IV trastuzumab 4 mg/kg, followed by 2 mg/kg IV weekly (149 patients); or lapatinib 1,000 mg/day with trastuzumab (152 patients), for a total of six weeks. Subsequently, patients continued with the same targeted therapy plus weekly paclitaxel (Taxol, Bristol-Myers Squibb) 80 mg/m^2 for another 12 weeks until definitive surgery (i.e., complete removal of the tumor).

After surgery, patients received three cycles of adjuvant fluorouracil plus epirubicin plus cyclophosphamide (FEC), followed by the same targeted therapy as in the neoadjuvant phase for a further 34 weeks to complete 52 weeks of anti–HER-2 therapy. The dose of lapatinib 1,000 mg/day in the combination arm was amended to 750 mg/day in 54 of 152 patients.

The primary endpoint was the rate of pathological complete response (pCR), defined by National Surgical Adjuvant Breast and Bowel Project (NSABP) guidelines as the absence of invasive cancer in the breast at the time of surgery. The women who were included had operable invasive breast cancer larger than 2 cm without evidence of metastases and with HER-2 overexpression and/or HER-2 gene amplification and known

estrogen receptor (ER) status. Actual tumor size was larger than 5 cm in approximately 40% of these women.

Treatment with the addition of both trastuzumab and lapatinib to neoadjuvant chemotherapy met its primary endpoint, with a pCR rate of 51.3%. By comparison, the pCR rate reached only 29.5% with the addition of trastuzumab alone (combination vs. trastuzumab alone, $P \leq 0.0001$) and 24.7% with the addition of lapatinib alone.

Results similarly favored dual HER-2 therapy in locoregional control, regardless of hormone receptor status. The pCR rate was highest for dual HER-2 therapy in hormone responsive–negative women (61.3%), compared with 41.6% for hormone responsive–positive women. Dr. Baselga noted that responses among patients with lowered lapatinib doses were similar to responses at higher doses.

Higher grades of diarrhea, hepatic abnormalities, neutropenia, and skin disorders, while generally manageable, were more common in the lapatinib arms.

Discussant Eric P. Winer commented: "In my view, trastuzumab plus lapatinib plus paclitaxel looks like a regimen that is of great interest."

Results of the 8,400-patient ALTTO trial (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) are eagerly awaited. ALTTO, which is currently accruing patients, includes a sequential arm, with patients switching from trastuzumab to lapatinib; separate lapatinib and trastuzumab arms; and the two arms combined.

Everolimus Plus Tamoxifen Versus Tamoxifen Alone In Patients Receiving Previous Aromatase Inhibitors: The TAMRAD Trial

• Thomas Bachelot, MD, Centre Leon Berard, Lyon, France

Dysregulation of the P13K/Akt/mTOR pathway has been found in a variety of cancer cells, and constitutively active P13K/Akt signaling has been identified as a major determinant of cell growth and survival in an array of cancers. Evero- limus (Afinitor, formerly RAD001, Novartis) demonstrates promising activity in an *in vitro* model of hormone resistance and has been shown to significantly increase the neoadjuvant antitumor activity of letrozole (Femara, Novartis). Although earlier randomized trials of first-line hormone therapy plus mTOR inhibition in metastatic breast cancer (mBC) have been disappointing, Dr. Bachelot said, selection of mBC patients previously treated with aromatase inhibitors may enrich the study population with subjects whose tumors are driven by activation of the P13K/Akt/mTOR pathway.

The goal of TAMRAD (tamoxifen/RAD001) was to estimate the clinical benefit rate (CBR) of the everolimus/tamoxifen combination in such a population after six months of treatment. Patients in TAMRAD were stratified by primary or secondary hormone resistance, as determined by early or late progression after prior aromatase inhibitor treatment. The women were randomly assigned, in a 1:1 fashion, to receive either tamoxifen 20 mg/day alone or everolimus 10 mg/day plus tamoxifen 20 mg/day.

Median age was 64 years (range, 41–86 years) among the 111 included patients. Prior aromatase inhibitors had been given to 34 patients (31%) in the adjuvant setting; to 67 patients (60%) in the metastatic setting, and to 10 patients (9%) in both the adjuvant and metastatic settings. The population was poorly hormone-sensitive; disease in all but 10 patients (9%) had progressed either during treatment with aromatase inhibitors within six months after adjuvant aromatase inhibitor treatment. Furthermore, 57 patients (51%) and 28 patients (25%) had received prior chemotherapy in the adjuvant and/or metastatic setting, respectively. The primary endpoint was the CBR (complete response plus partial response plus stable disease) at six months.

Patients were evenly divided between those with primary and secondary hormone resistance. In an exploratory analysis after a median follow-up of approximately 22.5 months, the CBR was 42.1% for the tamoxifen patients and 61.1% for the tamoxifen/everolimus patients ($P = 0.045$). Similarly, the time to progression (TTP) favored the combination group (tamoxifen, 4.5 months; tamoxifen/everolimus, 8.6 months) (HR = 0.53; CI, 0.35–0.81, exploratory log-rank: $P = 0.0028$), as did overall survival (HR = 0.32; CI, 0.15–0.68, exploratory log-rank: $P = 0.0019$).

Among patients with secondary hormone resistance (defined as late relapse after six or more months, or prior response with subsequent disease progression and metastasis after receiving aromatase inhibitors), the CBR differences were accentuated. The CBR in this group was 44.8% for tamoxifen and 77.8% for tamoxifen/everolimus.

Looking at TTP as a function of intrinsic hormone resistance, Dr. Bachelot noted that among patients with primary resistance, the TTP was 3.9 months for tamoxifen and 5.4 months for tamoxifen/everolimus (HR = 0.74). Among patients with secondary hormone resistance, the TTP was five months for tamoxifen and 17.4 months for tamoxifen/everolimus (HR = 0.38).

The incidence of adverse events, particularly fatigue, stomatitis, rash, anorexia, and diarrhea, was higher with the combination. Dose reductions were required in 28% of patients receiving the combination, but no dose reductions were necessary for those receiving tamoxifen. Discontinuations resulting from treatment-related adverse events, however, were higher with monotherapy (7% with tamoxifen; 5.6% with tamoxifen/everolimus).

The significance of the P13K/Akt/mTOR pathway, Dr. Bachelot said, is confirmed by TAMRAD results.

"It seems to be very important when [patients] respond to hormone therapy and then become resistant."

BOLERO (Breast Cancer Trials of Oral Everolimus), an everolimus phase 3 trial program in patients with locally advanced or metastatic breast cancer, is under way. ■